REMARKS/ARGUMENTS

Status of the claims

In the interests of expediting prosecution, claims 33 and 48 have been amended to recite that the reactivator displaces the inhibitor from the responder complex. This amendment adds no new matter. The amendment merely explicitly sets forth what was implicit in the claims. Support can be found, *e.g.*, in paragraph 75, lines 22-25; and paragraph 106.

Rejection of claims 33, 35, 37, 38, 50, 52, 63, 64, 66, and 67 under 35 U.S.C. § 103

Claims 33, 35, 37, 48, 50, 52, 63, 64, 66, and 67 are rejected as allegedly unpatentable over Balint, WO/0071702 ("Balint") in view of Nandabalan *et al.*, U.S. Patent No. 6,057,101 ("Nandabalan"); and further in view of Strynadka *et al., Nature* 368:657-660, 1994 ("Strynadka"); Wigley *et al., Nature Biotechnol* 19:131-136, 2001 ("Wigley"), and Anderson *et al.*, U.S. Patent No. 6,974,684 ("Anderson"). First, Applicants note that Anderson was not discussed in this particular rejection; the reference was only cited in the rejection of claims 36, 39, 51, and 54. Therefore, Anderson is not addressed in this section. Second, the rejection refers to Strynadka *et al., Nature Structural Biology* (page 5 of the final Office Action). A Strynadka reference was previously cited in the first Office Action on the merits, but that referenced the publication in *Nature* noted above. There has been no previous citation of Strynadka *et al, Nature Structural Biology* by the Examiner and it is not listed on the Notice of References cited. The rejection is therefore being construed as referring to the *Nature* reference. If this is incorrect, Applicants respectfully request that the Examiner provide the full citation.

The rejection

The Examiner cites Balint as teaching a fragment complementation system in which there are two fragments of a reporter. When the two fragments are together, the reporter is active. In Balint's system, one of the fragments is linked to one polypeptide and the other fragment is linked to another polypeptide. If the two polypeptides bind to one another, the fragments come together, thereby resulting in reporter activity. The Examiner states that Balint

does not teach the method where the polypeptide domains are linked to a reporter and an inhibitor of the reporter molecule and where a molecule that interferers with binding of the two polypeptides results in activation of the reporter. The Examiner then alleges that these missing elements are supplied by Wigley, Nadabalan and Strynadka.

Wigley is cited for teaching that there is a problem in fragment complementation with a constant background of spontaneous assembly. The Examiner therefore points to Wigley as reflecting a motivation to alter the fragment complementation system of Balint.

Nadabalan is cited as teaching a system where a transcription inhibition domain is fused to one protein and a cI DNA binding domain is fused to another protein. When the two proteins interact, the CI DNA binding domain oligomerizes sufficiently to cause DNA binding and inhibition of transcription. Nandabalan teaches that inhibitors that interfere with binding between the two proteins can be identified by activation of transcription. In the interpretation of Nadabalan set forth in the rejection (page 9 of the Office action), the Examiner consider the DNA binding domain "of a reporter" and the transcriptional activator/inhibition domain as an "auto-inhibited responder complex).

Strynadka is cited as teaching β-lactamase and an inhibitor of β-lactamase (BLIP).

The Examiner contends that it would have been obvious to employ expression vectors comprising: a nucleic acid encoding a first binding pair member linked to β-lactamase and a nucleic acid encoding a second binding pair member linked to a β-lactamase inhibitor protein, BLIP, where the β-lactamase molecule is inhibited when the binding pair members interact. A target molecule that binds to one of the binding pair members prevents BLIP from binding to the β-lactmase molecule thereby activating β-lactamase. Specifically, the Examiner alleges that it would have been obvious to modify Balint to use β-lactmase and BLIP in place of the two complementing β-lactamase fragments (to avoid constant background) because Strynadka teaches that inhibition of β-lactamses by BLIP. Nandablan is also cited in support of selecting a molecule that inhibits the interaction of the two binding domains, where the

interaction of the two binding domains is indicated by inhibition of the reporter molecule and the inhibition of the interaction of the two domains is indicated by an active reporter.

Applicants respectfully traverse the rejection. In order to establish a proper case of obviousness, the prior art must teach or suggest all of the claim elements. There must also be a reason to modify the references and there must be a reasonable expectation of success. The rejection fails to meet these criteria.

The cited art neither teaches nor suggests all of these claim elements.

Not all of the elements of the claims are accounted for in the rejection. Specifically, the rejection does not point to any teachings in the prior art relating to a reactivator complex. The current claims are drawn to methods that employ expression vectors encoding the following components:

Claim 33

- a competitor antibody
- a reactivator complex, which comprises:

  a reactivator molecule covalently linked to the target antigen
- a library encoding responder complexes, each of which comprises:

  a responder molecule covalently linked to an inhibitor and to a candidate antibody

Claim 48

- a competitor antibody
- a responder complex, which comprises:

  a responder molecule covalently linked to an inhibitor and to the target antigen.
- a reactivator molecule, which comprises:
- linked to a candidate binding molecule; and
- a library encoding reactivator complexes, each of which comprises

  a reactivator molecule covalently linked to a candidate antibody.

Applicants also direct the Examiner to paragraphs 75 and 106; as well as to Figures 3 and 4, which provide an exemplary embodiment of the invention. (Please note that the binding interaction detection system depicted in Figures 1 and 2 is not claimed in the claims under examination.)

In the current invention, an autoinhibited responder complex is the responder molecule that is covalently linked to the inhibitor and to a binding pair member. The responder therefore is inactive because it is covalently linked to the inhibitor. The reactivator complex comprises a reactivator that is covalently linked to another binding pair member (or candidate binding pair member). The responder molecule can be activated when the reactivator displaces the inhibitor from the responder. Thus, when the two binding pair members bind to one another, the reactivator is brought into proximity to the auto-inhibited responder and can then displace the inhibitor. The rejection does not include any teaching relating to a reactivator molecule.

Furthermore, in the current claims, in the responder complex there is covalent linkage of the binding pair member, the responder and the inhibitor. The rejection again does not cite any prior art as teaching or suggesting covalent linkage of the responder and inhibitor in a complex.

In view of the foregoing, the rejection fails to establish that all of the elements of the claims are taught or suggested by the prior art.

The proposed modification would not work in the claimed invention

The Examiner proposed modification also would not work in Applicants' invention. The Examiner is proposing that the first binding pair member would be linked to β-lactamase and the second binding pair member would be linked to an inhibitor of β-lactamase. However, in the current claims a binding pair member is covalently linked to both the inhibitor and the β-lactamase to make an auto-inhibited responder complex. If one of skill were instead to link either β-lactamase or the β-lactamase inhibitor to a second binding molecule (to which the reactivator is linked) the invention wouldn't work. A binding interaction between the two binding pair members would theoretically result in inhibition of the binding activity. However,

the reactivator molecule (which is also part of Applicants' invention and is linked to one of the binding pair members) would then lead to displacement of the inhibitor, which causes activity. So there would be no difference between the responder activity when the binding member interact (due to the presence of the reactivator) and when they don't interact. Accordingly, the proposed modification wouldn't reasonably be expected to work.

Furthermore, if one were to include the missing elements relating to covalent linkage, the proposed modification again wouldn't work. The claims recite that the inhibitor and responder are in a complex and are covalently linked in that complex. In the Examiner's proposed combination, covalently linking the inhibitor to the responder would not provide anyway of selecting for binding between binding pair members.

In view of the foregoing, claims 33, 35, 37, 48, 50, 52, 63, 64, 66, and 67 are patentable over the cited art. Applicants therefore respectfully request withdrawal of the rejection.

Rejection of claims 36, 39, 51, and 54 under 35 U.S.C. § 103,

Claims 36, 39, 51, and 54 are rejected as allegedly unpatentable over Balint in view of Nandabalan and further in view of Strynadka and Wigley; and further in view of Anderson. The examiner contends that it would have been obvious to use Fab fragments in the method of Balint because of the teachings of Anderson. Applicants respectfully traverse. The teachings of Balint, Nandabalan, Strynadka, and Wigley in combination do not arrive at Applicants invention for reasons explained above. Anderson does not cure the deficiencies in these primary references. The claims are thus patentable over the cited art. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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